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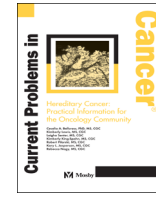

Epidemiology of advanced prostate cancer: Overview of known and less explored disparities in prostate cancer prognosis

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Racial disparities

Several studies have investigated potential explanations of the well-known disparate survival of African Americans with prostate cancer compared with white patients in the United States. Using data from the Detroit Surveillance, Epidemiology, and End Results (SEER) registry for the period 1988-1992, Schwartz et al. found that African American men with localized or regional prostate cancer had a 30% lower survival rate than their white counterparts. The corresponding difference in survival rates for those with distant disease was 75%.[1] These disparities in all-cause mortality were explained by socioeconomic status (SES) and treatment, but not by the differences in age and tumor grade. An earlier cohort study combined information from the US Census with the data from the San Francisco Bay Area SEER registry to assess survival among men diagnosed with prostate cancer between 1973 and 1993.[2] The California registry analyses were conducted using 2 end points: death due to prostate cancer and death due to other causes. The data indicated that differences in SES did not explain why African American men die of prostate cancer at a higher rate when compared with white men. By contrast, SES-associated differences appeared to explain almost all of the racial differences in risk of death due to other causes.[2]

To further address the contribution of various factors to differences in prostate cancer survival, Taksler et al estimated that choice of treatment and physician explained only approximately 17% of the racial gap in prostate cancer mortality. Socioeconomic factors and comorbidities explained an additional 15% and 4%, respectively, and the remaining disparity was attributable to tumor characteristics (50%) and other, yet unidentified, factors.[3] Powell et al compared prostate tumor characteristics among African American and white men representing 2 groups: those who died of causes other than prostate cancer, but were found to have the disease on autopsy, and those diagnosed with prostate cancer who underwent radical prostatectomy. Autopsy data indicated that pathologic characteristics of subclinical prostate cancer in African American and white men do not differ by race. Radical prostatectomy data, on the contrary, revealed that prostate cancers (measured by adding the volumes of the individual foci) tended to be larger and Gleason grade on average was higher in African American patients.[4]

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These results are in agreement with recent analyses of the national SEER data, which demonstrated that relative to their white counterparts, African American patients with prostate cancer are more likely to be diagnosed at a younger age, have a higher prostate-specific antigen (PSA) level at diagnosis, and have high-grade (Gleason score 8-10) disease.[5]

These population-based observations indicate that although SES and access to therapy undoubtedly explain some of the racial disparities in prostate cancer prognosis, there may be important tumor characteristics that differ in white and African American patients with prostate cancer. These findings are not limited to the United States and were confirmed in other countries including Great Britain,[6,7] France,[8] and Brazil.[9] However, it is also important to keep in mind that a large hospital-based cohort study in the United Kingdom found that after fully controlling for treatment and stage, race was no longer a predictor of survival or treatment outcomes.[10]

Prostate cancer disparities by place of birth among men of African descent

Several studies investigated the differences by place of birth or by country of residence among patients with prostate cancer of African descent. The data from the international cancer registries show that incidence of prostate cancer in black men residing in the Caribbean may approach and even exceed those reported among African Americans.[11,12] By contrast, the corresponding rates in Sub-Saharan Africa are reported to be several-fold lower[13] than the rates among African Americans, although recent hospital-based data from Nigeria indicate that the incidence in West Africa may be higher (perhaps as high as 100 cases per 100,000 person-years) than previously estimated.[14]

International variation in prostate cancer aggressiveness among men of African descent was examined in a study that compiled information from multiple of population- and hospital-based reports.[15] The proportion of cancers diagnosed at T1 category among African Americans ranged from 35%-63%, compared with 15%-29% in Sub-Saharan Africa, 24% in the Caribbean, and 34% in the United Kingdom. A significantly higher proportion of tumors in Africa had a high Gleason score or high tumor stage compared with those in the United States or the United Kingdom. PSA levels also differed across countries with the highest and the lowest median serum concentrations at the time of diagnosis reported in London, UK (107.6 ng/mL), and in the Northeastern US (5.9 ng/mL), respectively.[15]

Useful information can be obtained from studies comparing patients with prostate cancer of African descent who were born in different countries but reside in the United States. Mutetwa et al[16] used cancer registry data from Brooklyn, NY, to compare survival following prostate cancer diagnosis among African Americans, Caribbean-born immigrants living in the United States, and of men residing in Guyana or Trinidad and Tobago. The Caribbean-based patients were diagnosed at a later age and had a significantly lower 5-year survival compared with their counterparts who were treated in the United States. Importantly the 5-year survival of Caribbean-born patients living in the United States was not significantly different from that of African Americans indicating no inherent differences in disease aggressiveness or access to care.[16]

Another recent study compared tumor characteristics of 19,798 US-born, 267 Jamaican-born, and 246 West African–born men diagnosed with prostate cancer and reported to the SEER program between January 1, 2004 and December 31, 2009.[17] Among men with a known Gleason score, the percentages of advanced tumor grade (Gleason scores 7-10) were similar in all 3 study groups after controlling for diagnosis as a continuous variable, median county income, and receipt of radical prostatectomy. The distributions of PSA levels were also independent of the place of birth.[17]

On balance, these reports do not show that place of birth is an important determinant of disease aggressiveness among patients with prostate cancer of African descent (at least among men whose ancestry is linked to West Africa). However, definitive conclusions cannot be made owing to lack of large well-coordinated international studies designed to overcome problems of disparate data quality and take into account variability in clinical practices.

Gay, bisexual, and transgender persons—A large and understudied population group

The estimated annual numbers of newly diagnosed prostate cancers among men having sex with men (MSM) in the United States range from 4000-20,000,[18] yet very little information is available about the clinical characteristics and prognosis of prostate cancer in this population.[19] Only 1 study investigated the differences in physical health, diagnosis, and treatment outcomes in MSM and non-MSM patients with prostate cancer. Wassersug et al[20] compared MSM and non-MSM patients with prostate cancer and reported that cancer among MSM patients were characterized by significantly lower Gleason scores. The authors suggested that MSM patients were more likely to undergo regular health checkups.

An important health issue among MSM patients is the relatively high incidence and prevalence of human immunodeficiency virus (HIV) infections.[21] Although HIV carries a risk of specific malignancies such as Kaposi sarcoma and certain types of non-Hodgkin's lymphoma,[22] incidence of other cancers has been also been the area of concern.[19,23,24] The data on the association between HIV infection and prostate cancer are conflicting with some studies showing an increase in risk among HIV-positive relative to HIV-negative men,[19,25] and others showing no difference or even an inverse association.[26-28] A recent cohort study of men with clinical AIDS demonstrated the same prostate cancer incidence as in the general population during the pre-PSA time period (<1992), but a significant 2-fold reduction in risk during the PSA era (1992-2007). This reduction was only observed for local and regional stage prostate cancer, but not for distant stage disease.[28] Importantly, all-cause mortality rate increased by approximately 34% among patients with prostate cancer with clinical AIDS compared with the general population. The increase in mortality was particularly pronounced (almost 5-fold) among men with distant stage cancer.[28] These data indicate that prostate cancer is an important contributor to mortality among AIDS patients, although the specific mechanisms by which the risk of death is increased remain unclear.

Little information is available regarding the clinical characteristics of prostate cancer in HIV-infected men (regardless of sexual orientation). The available studies are single institution based and include no more than 20 patients. Despite these limitations, the available literature shows no evidence that HIV-infected patients with prostate cancer have more aggressive disease or experience worse prognosis compared with HIV-negative men. For example, Kahn et al compared 13 men with HIV to 26 control patients matched on age, race, stage, Gleason score, PSA level, and radiation treatment received. Both the groups had similar biochemical failure rates, and HIV-positive men had lower radiation toxicity scores than HIV-negative controls.[29] Two additional studies presented case series of HIV-infected patients with prostate cancer. Although no comparisons with HIV-negative populations were performed, these studies demonstrate that Gleason scores were similar to those expected in the general prostate cancer population and there was no evidence that treatment effectiveness was influenced by the HIV status.[30,31]

Another group that may represent an underserved population segment is transgender women. The terms “transgender” or “gender nonconforming” describe a heterogeneous group of persons who express a need to move across the culturally defined binary categories of gender. This group represents one of the most underserved and understudied segments of the US population.[32] The persistent need to transcend the gender boundaries is called “gender identity disorder” (GID), a condition characterized by desire to live and be accepted as a member of the opposite sex.[33] The prevalence of GID in the United States has been reported to range from 4.3-22.9 per 100,000 persons and appears to have been increasing over the last decade.[34]

Once GID-related sense of discomfort becomes so strong that it begins to dominate all aspects of life, a person may take steps toward achieving medical male-to-female (MTF) or female-to-male gender reassignment. The medical gender reassignment includes treatment with hormones of the desired gender, and surgical change of the genitalia or other sex characteristics termed “sex reassignment (or “sex confirmation”) surgery.”[35] Very little is known about the effects of contrasex hormones and sex reassignment surgery on the risk of age-related chronic conditions such as osteoporosis, diabetes, cardiovascular disease, and (with the

exception of anecdotal case reports and hypothetical discussions) no empirical data can be found on the risk of cancer.[36]

During hormone treatment, MTF individuals (transwomen) receive estrogen as well as an antiandrogen therapy, creating an environment in which the prostate is androgen deprived.[37] Hormone replacement therapy is continued after sex reassignment surgery and many transwomen continue it until death, fearing that the development of secondary sex characteristics may recede.[38] In surgical MTF transition, a gonadectomy, but not prostatectomy, is performed.[37] The prostate is not removed because the operation is cumbersome and comes with possible complications, including urinary incontinence.[39] The presence of the prostate in these women raises important questions regarding the influence of MTF gender reassignment on prostate cancer risk.

There are currently 7 case reports of transwomen who were diagnosed with prostate cancer.[40-46] Characteristics of prostate cancer cases reported among transwomen are summarized in the Table. Of the 3 cases with known Gleason scores, all had scores of 7 or higher. In 5 cases, the cancer had metastasized either at the time of diagnosis or following treatment. Two of the transwomen died owing to complications related to their prostate cancer, 2 were considered clinically stable, and the status of the other 3 remains unknown.

It is possible that prostate cancers developing in MTF individuals are more aggressive.[45] This hypothesis is supported by the elevated levels of PSA in most cases, which is a characteristic feature of an androgen-independent prostate cancer.[48] It should be kept in mind that all cases described in the literature presented because of clinical symptoms. It is therefore expected that their PSA levels were higher (range: 13.5-1710 ng/mL) than the levels typically observed in men diagnosed following screening.

Overall the effect of cross-sex hormones on prostate cancer remains unclear. Of the 7 cases, only 2 started receiving the cross-sex hormones before 45 years of age. It is possible that tumor development in these patients occurred before receiving hormone therapy.[45,46,48] It may be expected, although not demonstrated, that in the presence of high estrogen and low testosterone levels, prostate cancer risk in transgender persons may be lower than what is

Table
Characteristics of prostate cancer cases among reported among transwomen.

Reference	Age at diagnosis	Years since transition*	Stage at diagnosis	Gleason score	PSA at diagnosis	Treatment	Outcome
Turo et al[45]	75	31	Localized	7	13.5 ng/mL	External beam radiotherapy; antiandrogen treatment; palliative chemotherapy	Deceased
Molokwu et al[43]	60	41	Localized	N/A	N/A	Antiandrogen	N/A
Dorff et al[40]	78	23	Localized	9	20.6 ng/mL	Intensity-modulated radiation therapy; chemotherapy; maintenance adrenolytic therapy	Clinically stable
Miksad et al[42]	60	41	Localized	8	240 ng/mL	Antiandrogen treatment; radiation	N/A
Van Haarst et al[46]	63	12	Distant	N/A	1710 ng/mL	Monotherapy with estramurine	Clinically stable
Thurston[44]	64	12	Localized	N/A	27.3 ng/mL†	Radical radiotherapy	Deceased
Markland, 1975[41]	60	6‡	N/A	N/A	N/A	N/A	N/A

N/A, not available.
* Time calculated from start of hormone therapy unless otherwise indicated.
† Reported as ng/L (presumed to be a typo).
‡ Time calculated from sex reassignment surgery.

anticipated based on the average estimates in the general population of men.[47] On the contrary, recent evidence indicates that low testosterone level is not protective against prostate cancer[49] and suggests that low testosterone level may influence disease aggressiveness.[50,51]

As prostate cancers in transwomen may differ from those observed in the general male population, the protocol for screening should also be different. The most recent recommendations come from the Endocrine Society, which notes that a few key modifications should be added to the usual procedures.[52] These include the option of transvaginal palpation in addition to the standard annual rectal examination and an understanding that PSA levels may be uninformative as long-term exposure to estrogen can make these levels appear low.[37] It is important to keep in mind, however, that these recommendations are based primarily on expert opinion owing to lack of empirical data.

In summary, gay, bisexual, and transgender persons represent a sizeable, unique and largely understudied population. Understanding prostate cancer characteristics, prognosis and clinical care in this diverse community of patients is a recognized priority area in disparities research.[32] However, addressing the existing knowledge gaps may not be possible without well-supported, large-scale systematic studies.

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